IL-1beta-driven neutrophilia preserves antibacterial defense in the absence of the kinase IKKbeta.

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Public Summary:
The study showed that the immune system has an effective backup plan to protect the body from infection when the “master regulator” of the body’s innate immune system fails. The innate immune system defends the body against infections caused by bacteria and viruses, but also causes inflammation which, when uncontrolled, can contribute to chronic illnesses such as heart disease, arthritis, type 2 diabetes and cancer. A molecule known as nuclear factor kappa B (NF-kB) has been regarded as the “master regulator” of the body’s innate immune response, receiving signals of injury or infection and activating genes for microbial killing and inflammation. We studied the immune function of laboratory mice in which genetic tools were used to block the pathway for NF-kB activation. While prevailing logic suggested these mice should be highly susceptible to bacterial infection, the researchers made the unexpected and counterintuitive discovery that NF-kB-deficient mice were able to clear bacteria that cause a skin infection even more quickly than normal mice. We discovered that loss of NF-kB caused mice to produce a potent immune-activating molecule known as interleukin-1 beta (IL-1b), which in turn stimulated their bone marrow to produce dramatically increased numbers of white blood cells known as neutrophils. Neutrophils are the body’s front-line defenders against infection, capable of swallowing and killing bacteria with a variety of natural antibiotic enzymes and proteases.

Scientific Abstract:
Transcription factor NF-kappaB and its activating kinase IKKbeta are associated with inflammation and are believed to be critical for innate immunity. Despite the likelihood of immune suppression, pharmacological blockade of IKKbeta-NF-kappaB has been considered as a therapeutic strategy. However, we found neutrophilia in mice with inducible deletion of IKKbeta (Ikkbeta(Delta) mice). These mice had hyperproliferative granulocyte-macrophage progenitors and pregranulocytes and a prolonged lifespan of mature neutrophils that correlated with the induction of genes encoding prosurvival molecules. Deletion of interleukin 1 receptor 1 (IL-1R1) in Ikkbeta(Delta) mice normalized blood cellularity and prevented neutrophil-driven inflammation. However, Ikkbeta(Delta)Il1r1(-/-) mice, unlike Ikkbeta(Delta) mice, were highly susceptible to bacterial infection, which indicated that signaling via IKKbeta-NF-kappaB or IL-1R1 can maintain antimicrobial defenses in each other's absence, whereas inactivation of both pathways severely compromises innate immunity.